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Late Safety, Efficacy, and Cost-Effectiveness of a Zotarolimus-Eluting Stent Compared With a Paclitaxel-Eluting Stent in Patients With De Novo Coronary Lesions

2-Year Follow-Up From the ENDEAVOR IV Trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions)

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Objectives The aim of this study was to assess, after 2 years of follow-up, the safety, efficacy, and cost-effectiveness of a zotarolimus-eluting stent (ZES) compared with a paclitaxel-eluting stent (PES) in patients with native coronary lesions.

Background Early drug-eluting stents were associated with a small but significant incidence of very late stent thrombosis (VLST), occurring >1 year after the index procedure. The ZES has shown encouraging results in clinical trials.

Methods The ENDEAVOR IV trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions), a randomized (1:1), single-blind, controlled trial (n = 1,548) compared ZES versus PES in patients with single de novo coronary lesions. Two-year follow-up was obtained in 96.0% of ZES and 95.4% of PES patients. The primary end point was target vessel failure (TVF), and safety end points included Academic Research Consortium-defined stent thrombosis. Economic end points analyzed included quality-adjusted survival, medical costs, and relative cost-effectiveness of ZES and PES.

Results The TVF at 2 years was similar in ZES and PES patients (11.1% vs. 13.1%, p = 0.232). There were fewer myocardial infarctions (MIs) in ZES patients (p = 0.022), due to fewer periprocedural non–Q-wave MIs and fewer late MIs between 1 and 2 years. Late MIs were associated with increased VLST (PES: 6 vs. ZES: 1; p = 0.069). Target lesion revascularization was similar comparing ZES with PES (5.9% vs. 4.6%; p = 0.295), especially in patients without planned angiographic follow-up (5.2% vs. 4.9%; p = 0.896). The cost-effectiveness of ZES and PES was similar.

Conclusions After 2 years of follow-up, ZES demonstrated efficacy and cost-effectiveness comparable to PES, with fewer MIs and a trend toward less VLST. (The ENDEAVOR IV Clinical Trial: A Trial of a Coronary Stent System in Coronary Artery Lesions; NCT00217269) (J Am Coll Cardiol Intv 2009;2:1208–18) © 2009 by the American College of Cardiology Foundation

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Studies with Food and Drug Administration-approved drug-eluting stents (DES) with bio-stable polymers to deliver potent antiproliferative agents (sirolimus, paclitaxel, zotarolimus, and everolimus) have demonstrated an improvement in angiographic and clinical efficacy and comparable safety when compared with bare-metal stents (BMS) in randomized clinical trials after 1-year follow-up (1–6).

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However, unlike BMS, early versions of DES (sirolimus-eluting stent [SES] and paclitaxel-eluting stent [PES]) were associated with a disturbing complication, very late stent thrombosis (VLST), which occurred after the first year of DES implantation (7–9) and had previously only been observed after coronary vascular brachytherapy procedures (10,11). Although VLST after DES is a rare event, occurring at a frequency varying from 0.2% to 0.6%/year (8), the clinical significance cannot be discounted, because almost all patients suffer myocardial infarctions (MIs) or death. The VLST hazard might be constant for several years (12), and there is an increased sensitivity to antiplatelet therapy withdrawal (13–15). Thus, clinical practice must be modulated to account for possible VLST after DES, which has resulted in more selective DES use and prolonged dual antiplatelet therapy considerations (16,17).

The design characteristics of the zotarolimus-eluting stent (ZES) were intended to optimize patient safety. Experimental results in animal models have indicated that ZES has improved healing responses and restored endothelial function compared with SES and PES, more closely resembling a BMS (18–20). Surrogate safety end points in patients, with intravascular ultrasound, angioscopy, and optical coherence tomography, have also shown beneficial ZES responses compared with earlier SES and PES (21–24), and a pooled analysis with long-term follow-up of ZES-treated patients has indicated a frequency of VLST <1%, which is similar to results after BMS treatment (25,26). Initial findings from the ENDEAVOR IV trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Taxus Paclitaxel-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions) involving 1,548 patients with de novo native coronary lesions have demonstrated similar clinical safety and efficacy of ZES compared with PES during the first year of follow-up (5). The purpose of this report is to analyze clinical safety, efficacy, and cost effectiveness with extended 2-year follow-up in the ENDEAVOR IV trial.

Methods

Study design and patient population. The ENDEAVOR IV trial was a prospective, multicenter, single-blinded, randomized, controlled clinical trial that compared clinical and angiographic outcomes between patients treated with ZES and patients treated with PES. Consecutive adult patients with clinical evidence of ischemic coronary disease or a positive functional study were enrolled at 80 centers in the U.S. The institutional review board at each site approved the protocol, and each eligible patient provided written, informed consent before the index procedure.

Description of the key inclusion and exclusion criteria, study devices, and procedural-related details has been previously reported (5). After the interventional procedure, patients were evaluated at 30 days, 6, 9, and 12 months and yearly thereafter up to 5 years after the procedure. Patients in the angiographic and intravascular ultrasound subgroups were assessed at 8 months after the procedure. Dual antiplatelet therapy (aspirin and clopidogrel) was given for 6 months to all patients per protocol and continued thereafter, at the discretion of the managing physician.

Abbreviations and Acronyms

ARC = Academic Research Consortium
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
DRG = diagnosis-related group
MACE = major adverse cardiac events
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
QALY = quality-adjusted life year
ST = stent thrombosis
TLR = target lesion revascularization
TVF = target vessel failure
VLST = very late stent thrombosis
ZES = zotarolimus-eluting stent(s)

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Table 1. Baseline Clinical and Angiographic Characteristics of the Study Population

	ZES	PES	p Value
Patient demographics			
Age (yrs)	63.5 ± 11.1 (773)	63.6 ± 11.0 (775)	0.930
Male	66.9% (517/773)	68.5% (531/775)	0.514
Diabetes	31.2% (241/773)	30.5% (236/775)	0.783
Hypertension	79.4% (614/773)	82.6% (640/775)	0.120
Hyperlipidemia	81.4% (629/773)	84.8% (657/775)	0.078
History of smoking	62.6% (479/765)	60.4% (462/765)	0.401
Prior MI	21.1% (161/764)	23.2% (176/759)	0.324
Prior percutaneous coronary intervention	28.2% (218/773)	29.5% (229/775)	0.575
Prior coronary bypass surgery	9.8% (76/773)	8.4% (65/775)	0.332
Angina			0.367
Stable	45.6% (281/616)	47.9% (292/609)	
Unstable	51.6% (318/616)	49.9% (304/609)	
MI	2.8% (17/616)	2.1% (13/609)	
CCS class III or IV	50.3% (309/614)	47.9% (292/610)	0.392
Angiographic characteristics			
Target vessel			0.791
Left anterior descending	42.2% (326/772)	41.5% (321/774)	
Left circumflex	26.9% (208/772)	26.1% (202/774)	
Right coronary	30.8% (238/772)	32.4% (251/774)	
Type B2/C lesion	69.6% (537/772)	70.9% (549/774)	0.358
Number of diseased, native, major epicardial coronary vessels (>50% stenosed)			0.485
Single	54.9% (424/772)	57.2% (443/774)	
Double	28.6% (221/772)	26.1% (202/774)	
Triple	16.5% (127/772)	16.7% (129/774)	
Left ventricular ejection fraction (%)	57.3 ± 9.9 (760)	57.5 ± 10.3 (753)	0.745
Reference vessel diameter (mm)	2.73 ± 0.47 (772)	2.70 ± 0.46 (774)	0.197
Lesion length (mm)	13.41 ± 5.67 (771)	13.80 ± 6.09 (773)	0.199
Minimal lumen diameter (mm)	0.96 ± 0.40 (772)	0.93 ± 0.40 (774)	0.149
Diameter stenosis (%)	64.83 ± 13.29 (772)	65.68 ± 13.10 (774)	0.204

Values are % (n/total) or mean ± SD (n).
CCS = Canadian Cardiovascular Society angina class; MI = myocardial infarction; PES = paclitaxel-eluting stent(s); ZES = zotarolimus-eluting stent(s).

Clinical end points and definitions. The primary clinical end point in this clinical trial was target vessel failure (TVF), defined as the composite of cardiac death, MI, or clinically driven target vessel revascularization of the treated vessel at 9 months after the procedure. Pre-specified secondary clinical safety and efficacy end points included major adverse cardiac events (MACE), defined as death, MI, or clinically driven target lesion revascularization (TLR) (and individual component end points) and stent thrombosis (ST) at annual follow-up. Myocardial infarction was defined as either: 1) Q-wave MI requiring new pathologic Q waves in 2 or more contiguous electrocardiographic leads and either symptoms consistent with acute myocardial ischemia or elevation of cardiac biomarkers; or 2) non–Q-wave MI requiring elevated creatine kinase >2× the upper laboratory limit with elevated creatine kinase–myocardial band in the absence of pathological Q waves.

Stent thrombosis (both early and late) was adjudicated by a subcommittee of the clinical event committee, blinded to study stent identity and according to the definitions proposed by the Academic Research Consortium (ARC) (27).

Economic end points and analyses. In addition to clinical outcomes, an economic analysis was performed to determine the relative cost-effectiveness after treatment with ZES or PES. After identification of economic events with MACE- and adverse event-related hospital stays, adverse event system organ class designations were used to distinguish cardiac from noncardiac hospital stays, and Medical Dictionary for Regulatory Activities preferred terms were applied to differentiate types of cardiac hospital stays. Each study subject was assigned an index episode of care and a variable number of follow-up period episodes of care with a method that combined economic event data. Outpatient deaths were the only outpatient events.

Medical costs, length of stay, and quality of life estimates were assigned to episodes of care. The Centers for Medicare and Medicaid Services Medicare Severity Diagnosis Related Grouper was used to associate diagnosis-related groups

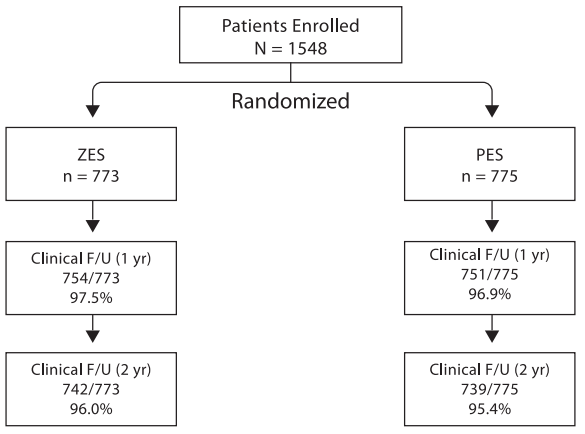

Figure 1. Patient Disposition and Follow-Up

Patients were randomized (1:1) to a zotarolimus-eluting stent (ZES) or a paclitaxel-eluting stent (PES). Patient follow-up (F/U) numbers for 1 and 2 years in each group are shown.

(DRGs) to episodes of care (28), and these assignments were then audited by a trained medical record professional. For cardiovascular episodes of care, medical costs and lengths of stay were estimated with Medicare national average payment amounts for 2008 (calculated with an average hospital Medicare base rate of $4,893) and arithmetic mean lengths of stay by DRG (29,30). For noncardiovascular episodes of care, medical cost and length of stay were assigned with Medicare national average relative weight and arithmetic mean length of stay. The DRG-specific costs for physician services were estimated with published sources and adjusted to 2008 values with the medical care component of the consumer price index (31). A $2,100 unit cost was assigned to both stent types (data on file, Medtronic CardioVascular, Santa Rosa, California). Because the type of repeat percutaneous coronary intervention procedure was not identified in the follow-up case report forms for this trial, results were extrapolated from the repeat percutaneous coronary intervention procedures performed at a single participating center (Duke University Medical Center, Durham, North Carolina) during the ENDEAVOR IV study period. These data were used to define the distribution of different types of percutaneous revascularization (32). Previously defined methods were used to assign quality of life weights (33), including a 0.79 quality-adjusted life year (QALY) adjustment for all revascularization procedures, a 0.85 QALY adjustment for coronary artery disease without revascularization, a 0.88 permanent QALY adjustment when subjects experienced a nonfatal MI, and a quality adjusted life day decrement for each day of estimated length of stay during a hospital stay (34).

Number of hospital stays (revascularization, other cardiac, noncardiac, and total), quality-adjusted survival (both undiscounted and discounted at 3%), and medical costs (both undiscounted and discounted at 3%) were computed as 2-year cumulative values by treatment (ZES or PES) with differences, 95% confidence intervals, and p values. Medical costs also were presented by annual time periods. Analyses were performed with generalized linear models on partitioned data with empirical standard errors and an adjustment for censoring. We then performed a comprehensive cost-effectiveness analysis to estimate the incremental medical costs/QALY saved with the use of ZES versus PES during the 2-year follow-up period. This cost-effectiveness ratio was calculated with the nonparametric bootstrap procedure, and results are shown as discounted mean values for the ratio.

Table 2. Clinical Outcomes at 2 Years

	ZES (n = 742)	PES (n = 739)	p Value
Death (all)	3.1 (23)	2.6 (19)	0.639
Cardiac	1.5 (11)	1.2 (9)	0.823
Noncardiac death	1.6 (12)	1.4 (10)	0.831
MI (all)	2.0 (15)	4.1 (30)	0.023
Q-wave	0.4 (3)	0.5 (4)	0.725
Non–Q-wave	1.6 (12)	3.5 (26)	0.022
Death or MI	5.0 (37)	6.5 (48)	0.221
Cardiac death or MI	3.4 (25)	5.1 (38)	0.096
Target lesion revascularization	5.9 (44)	4.6 (34)	0.295
Target vessel revascularization	8.9 (66)	9.2 (68)	0.857
Nontarget lesion, target vessel revascularization	4.2 (31)	5.8 (43)	0.154
Target vessel failure	11.1 (82)	13.1 (97)	0.232
Major adverse cardiac events	9.8 (73)	10.0 (74)	0.931

Values are % (n).
Abbreviations as in Table 1.

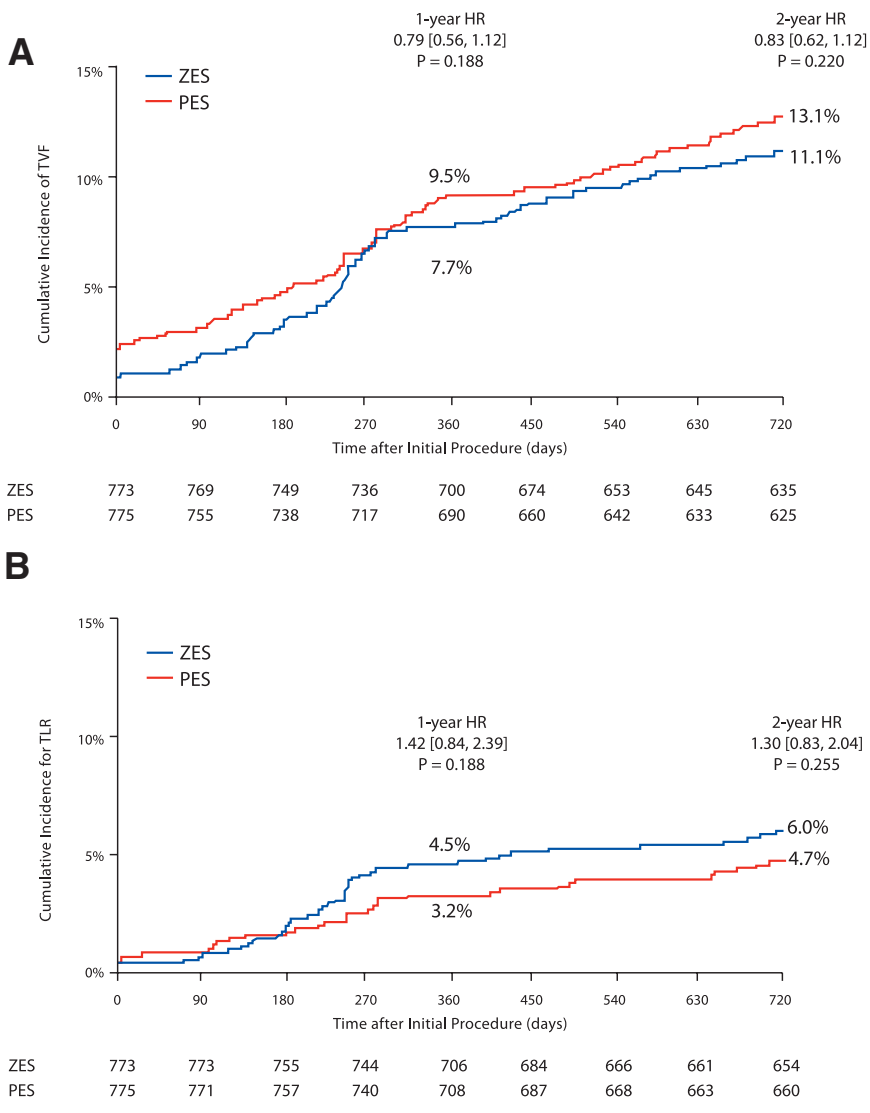

Figure 2. Cumulative Incidence of TVF and TLR at 2 Years

Hazard ratios (HR) with 95% confidence intervals and cumulative incidence of target vessel failure (TVF) **(A)** and target lesion revascularization (TLR) **(B)** at 1 and 2 years are displayed. Abbreviations as in Figure 1.

Statistical methods. The randomized ENDEAVOR IV trial was designed to compare the noninferiority primary end point (TVF at 9 months) between patients treated with ZES and those treated with PES (5). The primary objective of this analysis was to compare clinical safety and effectiveness outcomes between the 2 DES cohorts 2 years after the index revascularization.

Categorical variables were compared by the chi-square or Fisher exact test, as appropriate. Continuous variables are described as means with SD and were compared by unpaired *t* tests. Time-to-event data are reported and displayed as Kaplan-Meier estimates, with comparisons between groups by the log-rank test. All analyses are by intention-to-treat, with all patients randomized to each study stent included.

All analyses were performed with SAS software (version 8.2 or higher, SAS Institute, Cary, North Carolina). Data collection, clinical event adjudication, and analysis were performed at the Harvard Clinical Research Institute (Boston, Massachusetts). All authors had full access to the database and analysis upon which this manuscript is based.

Results

Clinical outcomes at 2 years. Baseline clinical and angiographic characteristics of the study population were similar

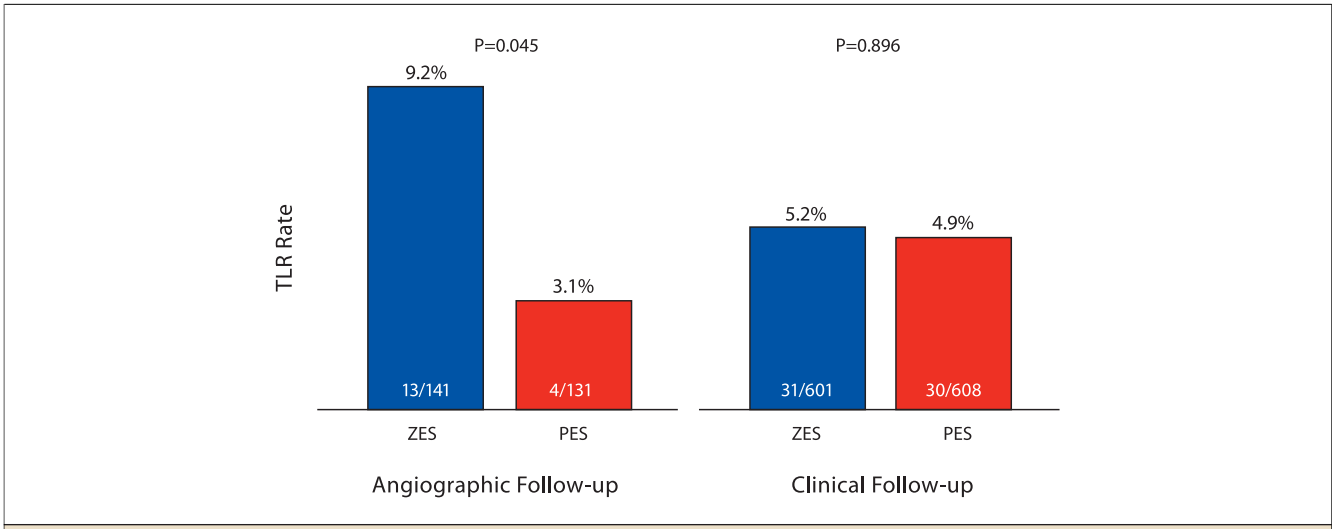

Figure 3. TLR by Angiographic and Clinical Follow-Up to 2 Years

Number and percent TLR for patients with angiographic follow-up and clinical follow-up at 2 years. Abbreviations as in Figure 1.

among ZES and PES patients (Table 1). Of the 1,548 patients enrolled in the ENDEAVOR IV trial, clinical follow-up was completed at 1 and 2 years in 97.5% and 96.0% of ZES patients and in 96.9% and 95.4% of PES patients, respectively, (Fig. 1). The primary study end point, TVF, was 11.1% for ZES compared with 13.1% for PES (p = 0.232) (Table 2, Fig. 2A). There were no differences in death, but there were significantly fewer non–Q-wave MIs in ZES versus PES patients (1.6% vs. 3.5%; p = 0.022, Table 2). There were no differences in overall clinically driven TLR or target vessel revascularization events comparing ZES with PES at 2 years (Table 2, Fig. 2B). In those patients with angiographic follow-up (18% of the total study population), TLR at 2 years was 9.2% for ZES and 3.1% for PES (p = 0.045) (Fig. 3). In those patients without angiographic follow-up, TLR was 5.2% for ZES and 4.9% for PES (p = 0.896) (Fig. 3).

ST WITHIN THE FIRST YEAR. Although there were no significant differences in early or late ARC ST during the first year of follow-up among the treatment cohorts, there was a trend toward more frequent ARC-definition (definite or probable) ST with ZES compared with PES (0.9% vs. 0.1%, p = 0.07). Of the 7 ZES patients with ARC ST (definite or probable), 3 occurred before 30 days (2 definite and 1 probable) and 4 occurred between 30 days and 6 months (3 definite and 1 probable). In the 3 ZES patients with ARC definite or probable ST before 30 days, 2 were associated with edge dissections and incomplete stent expansion, and 1 had an unplanned surgical procedure. In the 4 ZES patients with ARC definite or probable ST between 30 days and 6 months, 3 patients were no longer taking dual antiplatelet therapy (time of dual antiplatelet therapy cessation to ST was 2 days, 20 days, and 2 months); 1 of which also had an unplanned surgical procedure.

BETWEEN 1 AND 2 YEARS. Academic Research Consortium VLST (definite or probable) occurred in 1 ZES patient and in 6 PES patients (p = 0.069) (Tables 3 and 4, Fig. 4). The 6 PES ST events were associated with no deaths and 3

Table 3. Stent Thrombosis Through 2 Years

Outcome	ZES (n = 742)	PES (n = 739)	p Value
Early (0–30 days)			
Definite	0.3 (2)	0.1 (1)	1.000
Probable	0.1 (1)	0.0 (0)	1.000
Possible	0.0 (0)	0.0 (0)	—
Definite/probable	0.4 (3)	0.1 (1)	0.624
Any	0.4 (3)	0.1 (1)	0.624
Late (31–360 days)			
Definite	0.4 (3)	0.0 (0)	0.249
Probable	0.1 (1)	0.0 (0)	1.000
Possible	0.4 (3)	0.4 (3)	1.000
Definite/probable	0.5 (4)	0.0 (0)	0.124
Any	0.9 (7)	0.4 (3)	0.342
Very late (361–720 days)			
Definite	0.1 (1)	0.7 (5)	0.124
Probable	0.0 (0)	0.1 (1)	0.499
Possible	0.4 (3)	0.3 (2)	1.000
Definite/probable	0.1 (1)	0.8 (6)	0.069
Any	0.5 (4)	1.1 (8)	0.264
Cumulative (0–720 days)			
Definite	0.8 (6)	0.8 (6)	1.000
Probable	0.3 (2)	0.1 (1)	1.000
Possible	0.8 (6)	0.7 (5)	1.000
Definite/probable	1.1 (8)	0.9 (7)	1.000
Any	1.9 (14)	1.6 (12)	0.844

Values are % (n).
Abbreviations as in Table 1.

Table 4. ARC Definite/Probable Stent Thrombosis Up to 2 Years

DES	ARC Definition	Time to Event (Days)	Clinical Event	DAPT at Event
PES	Definite	413	Q-wave MI	ASA only
	Definite	495	Non–Q-wave MI	ASA + clopidogrel
	Definite	619	Non–Q-wave MI	ASA + clopidogrel
	Definite	645	Q-wave MI	ASA only
	Definite	689	Non–Q-wave MI	ASA only
	Probable	697	Q-wave MI	ASA + clopidogrel
ZES	Definite	369	Q-wave MI	None

ARC = Academic Research Consortium; DAPT = dual antiplatelet therapy; DES = drug-eluting stent(s); other abbreviations as in Table 1.

Q-wave and 3 non–Q-wave MIs, and 3 of the 6 patients were no longer receiving clopidogrel therapy (Table 4). The sole ZES VLST case was associated with a Q-wave MI in a patient who stopped taking both aspirin and clopidogrel 10 days before the ST event. The cumulative incidence of ARC definite or probable ST after 1 year mirrored the cumulative incidence of MIs after 1 year (Fig. 5).

Cost-effectiveness. There were no differences in quality-adjusted survival or medical costs (initially, during the second year, or cumulative during the 2 years of follow-up) between ZES and PES patient cohorts (Table 5). Similarly, bootstrap analysis of the 2-year cost-effectiveness showed no benefit of ZES compared with PES patients (Fig. 6).

Discussion

The key findings of the present analysis assessing clinical outcomes after 2 years in patients treated with ZES versus those treated with PES for single de novo coronary lesions from the randomized ENDEAVOR IV trial (1,548 patients with >95% follow-up) are: 1) up to 2 years after stent implantation, the ZES—compared with the PES—continued to demonstrate comparable clinical anti-restenosis efficacy; 2) ZES seemed to have a more favorable mid-term safety profile, with fewer episodes of VLST and significantly less MI in patients compared with PES; and 3) at 2 years, there was similar cost-effectiveness comparing ZES and PES.

Very late stent thrombosis and in-stent restenosis, the main 2 concerns after DES implantation, require meticulous long-term clinical follow-up to ensure patient safety and to determine whether overall clinical effectiveness is durable (7–9). Despite significantly higher 8-month angiographic in-stent late loss in ZES-treated patients, ischemia-driven TLR between 1 and 2 years were infrequent in the ENDEAVOR IV trial and similar for both ZES (1.6%) and PES (1.7%), and cumulative ischemia-driven TLR at 2 years was likewise similar for ZES (5.9%) and PES (4.6%). The clinical efficacy results for the ENDEAVOR IV trial at 2 years are consistent with multiple other ZES studies (35–39), suggesting the absence of a "late catch-up" phe-

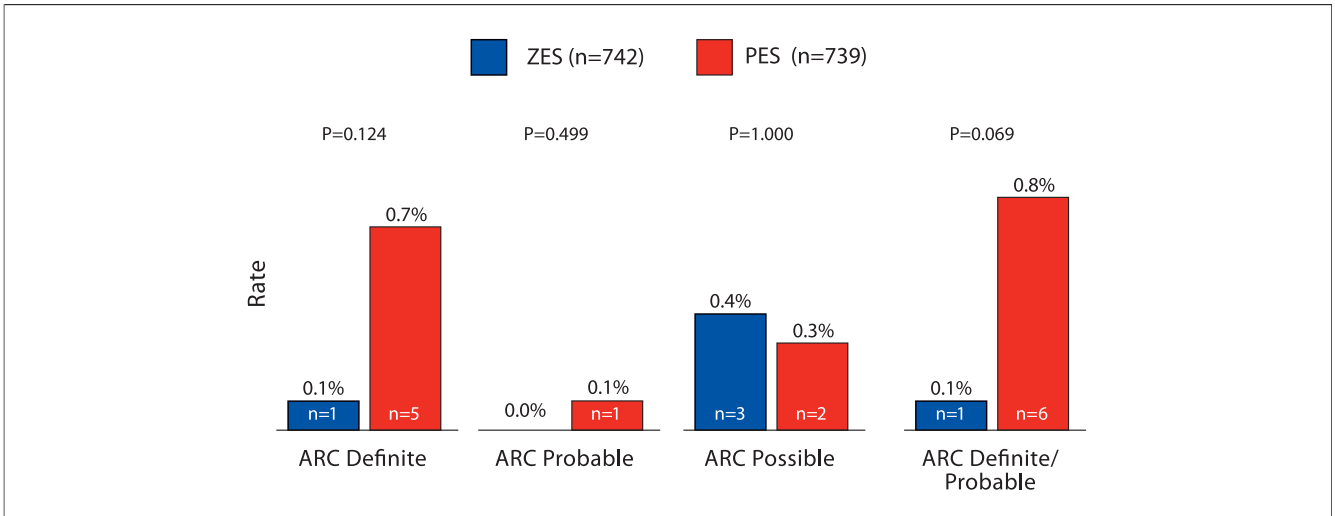

Figure 4. ARC-Defined Stent Thrombosis at 1 to 2 Years

Academic Research Consortium (ARC)-defined stent thrombosis rates for the second year after stent implantation. Abbreviations as in Figure 1.

Figure 5. Landmark Analysis of Incidence of Myocardial Infarction During the First Year and Between the First and Second Years After ZES and PES Implantation

The HRs with 95% confidence intervals for 0 to 1 year and 1 to 2 years are shown for the incidence rates of myocardial infarction. Abbreviations as in Figures 1 and 2.

nomenon and a durable effect on the reduction of clinical restenosis over time (26,38,40–42). Because recent reports have indicated concerns associated with increasing late loss and related late TLR events after 1 year with other DES (43,44), these ZES findings bear watching as further clinical follow-up is accumulated in the ENDEAVOR IV trial and other ZES clinical trials involving more complex lesion subsets (39,45). It is interesting to note that the 2-year results from the ENDEAVOR IV trial continue to emphasize the significant impact of angiographic follow-up on subsequent TLR events. In the subset of patients with planned angiographic follow-up, there were significant differences in 2-year TLR rates (ZES 9.2% vs. PES 3.1%, p = 0.045), whereas in those patients without angiographic follow-up (82% of the study population), there were no differences in 2-year TLR (ZES 5.2% vs. PES 4.9%, p = 0.896).

Because stent-related coronary thrombosis during the first year after implantation is known to be associated with multiple patient, lesion, and procedural predictors (25,46,47) that vary from study to study, we have emphasized the importance of very late (after 1 year) thrombosis events, which seem to be related to fundamental design characteristics of DES. The 2-year clinical outcomes from the ENDEAVOR IV trial reinforce the impression that ZES are similar to BMS from the standpoint of late safety, including VLST. However, it bears noting that the ENDEAVOR IV trial was not powered to demonstrate differences in safety end points such as cardiac death plus MI or ST, and after 2-year follow-up, the only statistically significant benefit of ZES over PES was a reduction in non–Q-wave MIs (3.5% vs. 1.6%, p = 0.022). Moreover, there are data from other recent randomized trials similarly underpowered to discern differences in ST, which compare ZES with other DES (both SES and PES) during the first year of follow-up. These studies show no consistent differences in ST during the first year of clinical follow-up (48,49). The largest randomized trial (8,800 patients, with enrollment

Table 5. 2-Year QA Survival and Medical Costs

	Taxus	Endeavor	Difference (95% CI)	p Value
Survival (days)	711.22	711.00	0.21 (−6.07 to 6.49)	0.95
Discount survival (days)*	690.09	689.89	0.20 (−5.85 to 6.24)	0.95
Quality-adjusted survival (days)	575.41	576.00	−0.60 (−5.95 to 4.75)	0.83
Discount QA survival (days)*	557.97	558.56	−0.59 (−5.74 to 4.56)	0.82
Medical costs ($)				
Initial year	17,713	17,167	545 (−178 to 1,269)	0.14
Second year	2,316	2,454	−137 (−782 to 510)	0.68
Cumulative 2-yr costs	20,029	19,621	408 (−632 to 1,269)	0.44
Cumulative discount 2-yr costs*	19,852	19,440	411 (−600 to 1,423)	0.43

*Discount rate of 3%/year.
CI = confidence interval; QA = quality-adjusted.

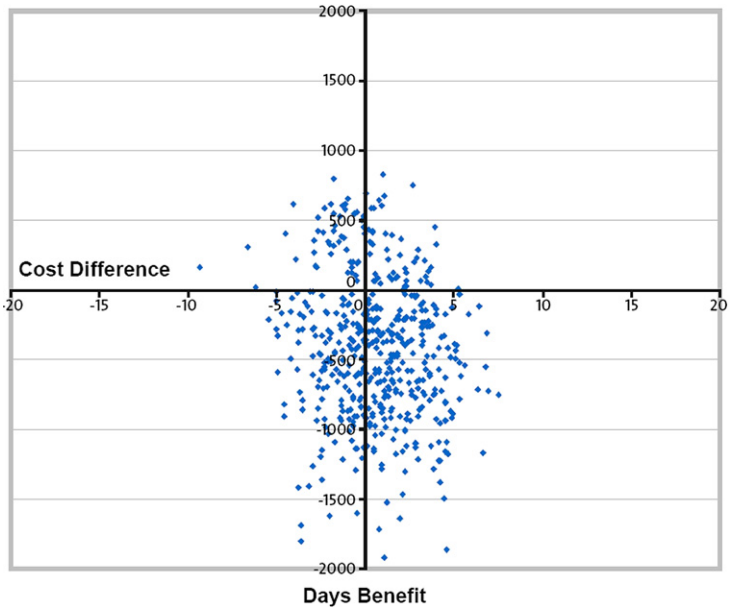

Figure 6. Bootstrap Results for the 2-Year Cost-Effectiveness

Results are shown as discounted mean values for the cost-effectiveness ratio.

completed) focusing on the comparative safety of ZES versus SES was designed to provide a more definitive answer to long-term (3-year) safety in a real-world patient population (45).

In the ENDEAVOR IV trial, there were more MIs in the PES group after 1 year due to a higher incidence of VLST events (1 event with ZES vs. 6 with PES). The 1 ZES patient with VLST had stopped taking both ASA and clopidogrel 10 days before the thrombosis event. These findings are similar to previous ZES studies versus BMS or SES (37,40,41). Moreover, a pooled analysis of all adjudicated ZES clinical trials with long-term follow-up indicated a VLST frequency of only 0.2% in over 2,000 ZES patients (26,42). Combined with higher rates of periprocedural MIs in PES patients, possibly related to increased side branch occlusions associated with PES stents (5,50), the overall early and late safety profile of ZES in the ENDEAVOR IV trial was favorable compared with PES.

The comprehensive cost-effectiveness analysis that was imbedded in the ENDEAVOR IV study design indicated no differences in quality-adjusted survival, medical costs, and cost-effectiveness, either acutely or at 2 years, comparing ZES versus PES treatment.

Study limitations. The patients and lesions treated in the ENDEAVOR IV study were not highly complex, and therefore, the results of this study cannot be extrapolated to patients with more complex coronary anatomy. This study was not designed or powered to compare rates of infrequent adverse clinical events such as death, MI, or ST; therefore, the results and trends should be interpreted as largely hypothesis-generating. Finally, longer follow-up is necessary to adequately assess late safety and efficacy events when comparing ZES and PES therapies.

Conclusions

This analysis of the ENDEAVOR IV trial demonstrates that the initial comparable clinical efficacy of ZES compared with PES is sustained at 2 years, with a similarly low rate of TLR and no differences in either TVF or MACE. Comparable clinical outcomes resulted in similar 2-year cost-effectiveness. These findings, coupled with the low incidence of VLST and lower incidence of MI after ZES versus PES implantation, provide evidence supporting the mid-term safety and efficacy of ZES in the treatment of de novo lesions in native coronary arteries. Longer follow-up of the ENDEAVOR IV trial and confirmation from additional randomized trials are necessary to substantiate these findings.

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